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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,929	01/08/2004	Knut-Egil Loekling	PN0301	5513

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Amersham Health, Inc.
IP Department
101 Carnegie Center
Princeton, NJ 08540

EXAMINER	
BARHAM, BETHANY P	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
10/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/753,929	LOEKLING ET AL.	
	Examiner	Art Unit	
	Bethany P. Barham	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-17 and 19-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-17 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt of Applicants Claim Amendments and Response filed on 09/10/2007 are acknowledged. Claims 1-13, 15-17 and 19-22 are pending. Claims 1-13, 15-17 and 19-22 are rejected.

Due to Applicants Amendments the 112 2nd and 102 rejection are hereby withdrawn. All other rejections of record are hereby maintained.

NEW REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 15-17, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,096,720 ('720) Love et al.

The limitations of the claims 1-6 are taught:

- '720 teaches sterically stabilized liposomes comprising a phospholipid having an amino head group such as phosphatidylethanolamine, such as dimyristoyl phosphatidylethanolamine, distearoyl phosphatidylethanolamine, etc., which can

be derivatised with polyethylene glycol and an acylglycerol lipid having at least 12 carbon atoms such as myristoyl, palmitoyl, etc groups and one acyl group such as 1,2-dipalmitoyl-sn-3-succinyl glycerol (claims 1, 17-22, 30-32, 34, and 37-39 and col. 7, line 37-col. 8, line 62).

- The polyethylene glycol derivatised phosphatidylethanolamine comprises 1-20% mole of the total lipid content (claim 23).

The limitations of claims are 15-17, and 22 are taught:

- A method of treating mammalian cancer and/or inhibiting expression in tissues or cells which comprises administering a composition according to claim 1 (a drug containing liposome) to a mammal in need of such a treatment (claims 1 and 43-44). The invention of '720 teaches oligonucleotide-containing liposomes prepared using known methods of preparation of drug-containing liposomes, and treatment of diseases such as mammalian cancer, particularly human cancer such as lung, stomach, renal, breast, laryngeal, pancreatic, colorectal cancers and malignant melanoma (col. 9, lines 16-60).
- '720 does not teach a single liposome comprising (i) a phospholipid having an amino head group such as phosphatidylethanolamine (dimyristoyl phosphatidylethanolamine, distearoyl phosphatidylethanolamine), (ii) phospholipid derivatised with polyethylene glycol and (iii) an acylglycerol lipid having at least 12 carbon atoms such as myristoyl, palmitoyl, etc.

However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the components of two working liposomes as taught by

'720 in order to obtain a liposome with components i, ii, and iii. '720 teaches liposomes as preferred embodiments comprising i and ii or i and iii. '720 teaches that these liposomes are 'comprising' meaning that any other component may also be included, since ii is taught to be included in the liposomes of '720 and i and iii are taught to be part of preferred embodiment it would have been prima facie obvious to look to '720 for how to make a composition comprising i, ii and iii, since all are known parts of a liposome used to target tumors.

MAINTAINED REJECTION

Claims 1, 7-13, 15-17 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,096,720 ('720) Love et al in view of US 6,159,445 ('445) Klaveness et al.

The limitations of claims 1, 7-12, and 20-21 are taught:

- '720 is taught above and teaches liposomes comprising (i) phosphatidylethanolamine such as dimyristoyl phosphatidylethanolamine, distearoyl phosphatidylethanolamine, etc., which can be (ii) derivatised with polyethylene glycol and (iii) an acylglycerol lipid having at least 12 carbon atoms such as myristoyl, palmitoyl, etc groups and one acyl group such as 1,2-dipalmitoyl-sn-3-succinyl glycerol (claims 1, 17-22, 30-32, 34, and 37-39 and col. 7, line 37-col. 8, line 62).

- '720 does not teach all three components (i-iii) in a single liposome nor does it teach imaging or contrast agents.
- '445 teaches that is it known in that art that contrast agents are used for imaging enhancement in X-ray, MRI, ultrasound, and nuclear medicine and are in a carrier matrix or encapsulated in liposomes (col. 1, line 17-col. 2, line 2). '445 teaches that fluid containing liposomes cause contrast enhancement in light imaging methods and are useful in vivo diagnostic light imaging (col. 7, line 56-col. 8, line 18). The invention of '445 comprises a medium for imaging modalities comprising liposomes which are known to be suitable for MRI, X-ray, ultrasound imaging containing contrast agents such as paramagnetic ions, metal chelates, paramagnetic and/or superparamagnetic agents, iron chelates, iodine, etc (col. 13, line 20-col. 14, line 25). '445 teaches that the liposomes can carry photolabelled particles (col. 10, lines 55-58).

The limitations of claims 13, 15-17, 19 and 22 are taught:

- In vivo studies are shown in Example 25 of iodixanol containing liposomes and results in enhancement of scattering in the tumor. '445 teaches that liposomes are known to deliver imaging agents to tumors and that imaging modalities containing liposomes are also suitable for controlled extended release of active compounds (col. 13, lines 55-65 and col. 14, lines 1-7).
- '445 teaches administration to human or animal of the above imaging particles may be formulated in a liposome for the in vivo light imaging of tumors, organs, ducts, etc (claims, 1 and 14 and col. 18, lines 27-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of '720 and '445. One of ordinary skill in the art would have been motivated to combine since both teach liposomes and therapeutic agents. '720 teaches liposomes as preferred embodiments comprising i and ii or i and iii. '720 teaches that these liposomes are 'comprising' meaning that any other component may also be included, since ii is taught to be included in the liposomes of '720 and i and iii are taught to be part of preferred embodiment it would have been prima facie obvious to look to '720 for how to make a composition comprising i, ii and iii, since all are known parts of a liposome used to target tumors. '720 teaches the specific liposome that is claimed by applicant for therapeutic use in tumors, while '445 teaches that several contrast agents are known for use in treating and imaging tumors (nuclear medicine and MRI, ultrasound, etc). As such one of ordinary skill in the art seeking to treat a mammalian subject with a pH sensitive therapeutic liposome of '720 would know how to image and treat the tumor using liposomes by looking to '445.

Response to Arguments

Applicant's arguments with respect to claims 1-13, 15-17 and 19-22 have been considered but not persuasive and are moot in view of the new grounds of rejection necessitated by applicants' amendments. Applicant's argue that because '720 only teaches liposome embodiments of instant claim 1 features (a) and (a*) or (a) and (b), but not a combination of (a), (a*) and (b) that the art does not apply to the present

application. However, the examiner respectfully points out that both of the preferred liposomes taught by '720 are for targeting tumors and (a), (a*) and (b) are all taught to be capable of forming liposomes which successfully target tumors by '720. '720 teaches that the preferred embodiments are 'comprising' and the open language does not exclude including other components, since (a*) is taught by '720 as being capable of forming liposomes which successfully target tumors it would have been obvious to add it to the preferred embodiment (a) and (b) as taught by '720 (also true with (b) and the (a) and (a*) embodiment).

Applicant further argues against '720 by stating that the liposomes of '720 are required to be 'sterically stabilized' while the instant claims are directed to pH sensitive liposomes. The Examiner does not disagree, however the components of the instant claims and the components of the art are the same (a, a*, and b forming a liposome) and as such would provide the same physio-chemical properties. Applicants own specification teaches in Example 1 liposomes with only components (a) and (b), as being pH sensitive liposomes and remain pH sensitive upon administration and so it is apparent that the liposomes of '720 are also pH sensitive and would remain pH sensitive upon administration, and this argument is not persuasive. It is not novel or inventive to claim a characterization or property of a previously patented and known composition. Furthermore, Cited as Interest it is known in the state of the art that liposomes modified with PEG provide longevity in vivo and cause prolonged blood residence time (see abtract of Weissig et al, "Long-circulating gadolinium loaded liposomes: potential use for magnetic resonance imaging of the blood pool" 2000)

Applicant's argue that there is no prima facie case of obviousness and no motivation to combine '720 and '445, and the examiner respectfully points out that applicant's argue against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It should be noted that the motivation to combine references can be different from the ones set forth by Applicant. That is, as long as motivation exists to combine the elements, the problem to be solved does not have to be 'use' of the liposomes taught by '720. As such, the examiner respectfully submits that there is motivation to combine the teachings of '720 and '445 since both teach liposomes as targeted therapeutic agents in tumors and the expected result of a liposome of '720 for targeting tumors (taught by both '720 and '445), also comprising well known contrast agent for treating and imaging tumors as taught by '445.

CITED AS INTEREST

Weissig et al, "Long-circulating gadolinium loaded liposomes: potential use for magnetic resonance imaging of the blood pool" teaches it is known in the state of the art that liposomes modified with PEG provide longevity in vivo and cause prolonged blood residence time and are useful as MR imaging agents (abstract).

Conclusions

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bethany Barham whose telephone number is (571)-272-6175. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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